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ROBERT H RINES
RINES AND RINES
ATTORNEYS AT LAW
81 NORTH STATE STREET
CONCORD, NH 03301

EXAMINER	
SOUAYA, JEHANNE E	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/306,333	VIJG, JAN	
	Examiner	Art Unit	
	Jehanne E Souaya	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *16 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-17* is/are pending in the application.

4a) Of the above claim(s) *7-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-6 and 10-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Currently, claims 4-17 are pending in the instant application. Claims 7-9 are withdrawn from consideration as being drawn to a non elected invention. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The amendment to the claims has rendered moot the rejections under 35 USC 112, made in the previous office actions. The following objections and rejections are either newly applied or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is NON-FINAL.

2. **NOTE**: Applicant should note that the following deficiencies were found with regard to the submission of the claims:

1) The recitation of the claims under consideration in the response filed April 16, 2003 contains clerical errors with regard to claims 5 and 6, which were not amended. The subject matter contained in claims 5 and 6 presented in the reply does not reflect the subject matter that is currently under consideration for claims 5 and 6. Specifically, the subject matter of claim 6 as presented in the April 16, 2003 reply is subject matter that has been withdrawn from consideration as being drawn to a non elected invention. The subject matter of claim 5 presented in the April 16, 2003 reply should be in claim 6. The subject matter for presently pending claims 5 and 6 can be found in the amendment filed October 25, 2000. As this appears to be a clerical error, claims 5 and 6 have been treated as they appear in the October 25, 2000 amendment.

2) The recitation of claims 1-3 as withdrawn is also in error as these claims were canceled in the amendment filed October 25, 2000.

Applicant should take care to include the proper status of the claims as well as correctly identify the subject matter of the claims currently under consideration in any subsequent reply to this office action.

New Grounds of Objection and Rejection

3. Claim 11 is objected to because of the following informalities: the claim fails to end in a period. Appropriate correction is required.

4. Claims 4-6 and 10-17 are objected to because the claims refer to sequences from tables when they could be referred to by SEQ ID NOS.

MPEP 2173(s) states "Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience."

Specification

5. The amendments filed October 25, 2000 and April 16, 2003 are objected to under 35 U.S.C. 132 because they introduce new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: With regard to short distance PCR primers for BRCA1, the originally filed specification listed a claim name next to a specific primer sequence (see p. 10 of specification as originally filed), however neither a SEQ ID NO nor an actual sequence were taught corresponding to the clamp name. Further, the clamp names do not appear (GC3, GC13, GC12, etc) do not correspond to the names given the actual GC

clamps set forth in the specification as originally filed. Consequently, the pairing of a SEQ ID NO corresponding to a GC clamp with a primer sequence in table 4 (added in the October 25, 2000 amendment, and amended in the April 16, 2003 amendment) adds new matter to the specification.

Applicant is required to cancel the new matter in the reply to this Office Action.

Response to Arguments

The response does not address this new matter rejection which was set forth in the previous office action. Applicant is required to cancel the new matter in reply to this Office Action.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 12 as amended, recites "... split 16 times to produce fragments numbered 11.1 through 11.16 *before said short distance multiplex PCR*". Such recitation is not supported by the specification as originally filed. The originally filed specification teaches that the splitting of

exon 11 into 16 fragments is carried out using short distance multiplex PCR using primers. The specification does not teach or suggest splitting exon 11, 16 times before short distance multiplex PCR. Further, considering the teachings of the specification as a whole, it is clear that the only method taught or suggested is a method which involves long range PCR to amplify large fragments of a gene, following by short range PCR using primers and GC clamps to generate smaller fragments that are then applied to two dimensional gel electrophoresis to detect mutations in the gene. The specification does not teach a method that excludes short range PCR to generate small fragments that are subsequently applied to two dimensional gel electrophoresis, and consequently, the specification fails to provide adequate support that applicant had possession of the claimed invention at the time the application was filed.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 10-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 as amended, in step a, recites a set of primer pairs to produce a first of amplification products with corresponding exon fragments, however, the number of primer pairs does not correspond to the number of exon fragments listed. Therefore it is unclear if the primer pairs listed are responsible for only the exon fragments listed, or if additional exon fragments were also generated. For example, the exon fragments generated in the long range PCR do not

include exons 5-13. Further, exon 20 is listed twice, and it is unclear whether parts of exon 20 are present in both fragments, or if this is in error?

Claim 12 as amended, recites "... split 16 times to produce fragments numbered 11.1 through 11.16 before said short distance multiplex PCR". It is unclear how the method of claim 10 is further carried out given this limitation in claim 12 with regard to exon 11. Claim 10 stipulates that during the short distance multiplex PCR, GC claims are attached to the primers of step b and the 2nd set of amplification products are subjected to two dimensional gel electrophoresis. However, if exon 11 is split without the use of primers, it is unclear what the primers of claim 10 would be used for since exon 11 would already be split into the appropriate fragments, and further, how the analysis step or the GC clamps which are specifically recited in claim 10 would be used with regard to exon 11. The method of claim 12 appears to be contrary and not usable with the method of claim 10, and is further not supported or defined by the specification as originally filed. Consequently, the metes and bounds of claim 12 are unclear.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 10-11, 13-14 and newly added claims 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vijg, Jan (WO 96/39535 referred to as Vijg) or in the alternative

Vijg et al (referred to as Vijg II, US Patent 6,007,231), each in view of Shattuck-Eidens et al (US Patent 5,693,473, referred to as Shattuck-Eidens).

One of the applied references has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Vijg teaches a method for diagnostic testing of DNA using PCR amplification followed by electrophoretic separation (TDGE) of the resulting fragments to detect possible gene variants of mutational defects (see abstract), specifically in the retinoblastoma gene. Vijg teaches that with the method, it is possible to test an individual at any time for inherited gene-encoded predispositions to disease, including late onset diseases such as cancers and neurodegenerative

diseases (see p. 3, lines 1-8). The method taught by Vijg comprises amplifying regions of target DNA, usually protein coding regions (exons), by PCR (see p. 6, lines 20-23) using primers which have been positioned to cover the exons. Vijg teaches that these amplification reactions are conducted separately, eg., if 27 exons in a gene are being analyzed, then 27 separate PCR reactions must be conducted, but also teaches that it is usually possible to conduct a few PCR reactions together in one tube (see p. 7, first para). Vijg then teaches that primers for short PCR are positioned such that a) the desired target sequences should be covered by amplicons of between 100 and 600 bp, b) amplicons should have optimal melting behavior, ie: consist of one lowest melting domain in addition to the GC-clamp attached to one of the primers, c) optimal amplicon distribution over a 2D gel, and d) similar reaction kinetics (See table 1, p. 13). Vijg then teaches that the PCR conditions are set up separately for each primer set with the long-PCR products as template for the short PCR and that multiplex co-amplification conditions are developed by grouping primer sets and adjusting reaction components. After the PCR, Vijg teaches that the mixture of fragments are subjected to 2-D electrophoresis in a denaturing gradient gel (see p. 16, lines 16-20) (TDGE based on DGGE). Vijg specifically teaches ways of improving TDGE (pp 6-9), for example a) positioning primers so that exons, splice sites, and regulatory regions are amplified, b) positioning primers so that non-specific amplification at other sites than the target sequences does not occur, c) for multiplexing, primers are selected so that predicted hybridization kinetics are similar to those of other primers in the multiplex reaction, and d) limiting the size of fragments for TDGS to 100-600 base pairs on average. Vijg further teaches that the method is new and improved (p. 10, line 18), has promise for becoming a

cost effective and widely accepted DNA diagnostic system (p. 5, lines 21-22), and is efficient and accurate in examining mutations (p. 2, lines 5-6).

Vijg II teaches a computer assisted method that enables a user to apply the method taught by Vijg outlined above, in a more rapid way (see col 4) through computer software aided selection of optimal sets of conditions (for example primer length, fragment size, GC clamp; see cols 6-7) among the large number of possibilities available.

Although neither Vijg nor Vijg II teach specific primers for use in the method to detect BRCA1 mutations, Vijg II teaches an example of how a BRCA1 mutation would appear on a 2 dimensional gel (fig 2) and Vijg teaches that the method can be applied to any gene, including those linked with cancer. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the method of Vijg or Vijg II to detect BRCA1 mutations as Vijg and Vijg II both teach the applicability of the invention with regard to any gene, including those linked with cancer, and Vijg II suggests to use such with the BRCA1 gene. Vijg II further teaches that method can be applied to any gene whose sequence is known (see col 5). Although neither Vijg nor Vijg II teach the sequence of the BRCA1 gene, the sequence was known in the art at the time of the invention by Shattuck-Eidens (see fig 10, SEQ ID NOS 14-34). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to use the method taught by Vijg or Vijg II with the BRCA1 gene taught by Shattuck-Eidens for the purpose of detecting BRCA1 mutations linked to cancer for the obvious improvement of providing a rapid test for identifying cancer associated mutations in BRCA1. The ordinary artisan would have had a reasonable expectation of success that using the method taught by Vijg, or Vijg II, primers could be generated that would both successfully

amplify the necessary coding regions of the BRCA1 gene and provide characteristic 2-D spot patterns for certain mutations as Vijg and Vijg II both teach in extensive detail (see pp 7-10, 18-19 of Vijg; and col.2, col.6, col.9, and claim 1 of Vijg II) how to prepare primers that would be successful in the method taught by Vijg given a known gene sequence and using long distance and short distance multiplex PCR. Using the references of Vijg or Vijg II, the ordinary artisan would have been motivated to develop primer sequences using the directions of Vijg and routine experimental manipulation for use in the method of Vijg or Vijg II in view of Shattuck-Eidens. Such primers are considered functionally equivalent to the primers of the present invention, absent secondary considerations, because the disclosure of Vijg and Vijg II teach in specific detail how to pick specific primer pairs, how to determine appropriate lengths for amplification products, and how to use GC clamping sequences to reliably detect genetic mutations in already known genes.

With regard to claim 13, which recites "a pair of clamping sequences" it is noted that Vijg II teaches (claim 2 of Vijg II) a method in which, in the event of overlap clustering of PCR fragments along the one dimension, changing the position of primers and/or changing the size of the GC clamp sequences. Vijg II further teaches (claim 5 of Vijg II) a method in which varying of the length of the GC clamp letter sequence is effected by adding a second GC clamp sequence. Thus Vijg II expressly teaches using two clamping sequences in the event of overlap clustering of PCR fragments. It is further noted that Vijg teaches that GC clamps are essential to guarantee the highest sensitivity to detect mutations in the denaturing gradient gel. Thus, it was known in the art at the time of the invention that using a GC clamp was important for highest sensitivity. It would have also been prima facie obvious to one of ordinary skill in the art at the time the

invention was made to provide a second GC clamp for the purposes of increasing sensitivity as it was known in the art that a GC clamp improved sensitivity of denaturing gradient gels. The courts have held that "it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the same purpose... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) [see MPEP 2144.06]. See further In re Harza, 274 F.2d 669, 124 USPQ 378 (CCPA 1960) [MPEP 2144.06 VI.B] regarding duplication of parts.

12. Claims 4-6 and newly added claim 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over of Vijg, Jan (WO 96/39535 referred to as Vijg) or in the alternative Vijg et al (referred to as Vijg II, WO/98/06872; Feb. 19, 1998), each in view of Shattuck-Eidens et al (US Patent 5,693,473, referred to as Shattuck-Eidens) as applied to claims 10-11, and 13-16 above, and further in view of Ahern, (The Scientist, vol. 9, July 24, 2995, from the Internet, pages 1-5).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the

application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

With regard to claims 4-6 and 17, although Vijg or Vijg II in view of Shattuck-Eidens, do not teach primer pairs in kit format, Ahern teaches that premade reagents and kits are convenient and save time (p. 4, 2nd para). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to package primers for amplification and detection of the BRCA1 gene in kit format, along with appropriate gel or gel materials and reagents for use in the method as taught by Vijg or Vijg II, for the purpose of providing premade kits to practice the method of Vijg or Vijg II in view of Shattuck Eidens for the obvious improvement of having the reagents in a convenient format that would save the ordinary artisan time in practicing the method of Vijg or Vijg II in view of Shattuck -Eidens.

Response to Arguments

The response traverses the rejection. The response argues that the Office has admitted that neither Vijg, Vijg II, Park, Liskay or Ahern teach the specific primer pairs of the instantly claimed invention, and yet applies such references as making the instantly claimed invention obvious to the ordinary artisan. This argument is moot with regard to the teachings of Park and

Liskay as these references are no longer applied (neither taught the sequence of the BRCA1 gene). The rejections stand with regard to the method of Vijg or Vijg in view of Shattuck-Eidens and further in view Ahern for the following reasons. The rejections above set forth that Vijg teaches a general method of detecting mutations in genes, such as those linked to cancer, comprising performing a long distance PCR to cover exons of the gene followed by a short distance multiplex PCR with primers and GC clamps to obtain amplicons of a certain size which could be applied to two dimensional gel electrophoresis to obtain a characteristic spot pattern for mutations within the gene. Vijg teaches such a method with regard to the Rb gene. Further, Vijg goes into detail with regard to generally, where primers should be placed for both long distance and short distance PCR, as well as the need for GC clamps and gel electrophoresis conditions (see pp 7-9). Additionally, Vijg II goes into even more detail with regard to optimizing conditions to achieve primers and GC clamps for use in the method and teaches a computer assisted method for picking optimal primers and GC clamps. Neither Vijg nor Vijg II limit the application of the method to only the Rb gene, or any gene in particular but teach that such would be useful to detect mutations in any gene, for example, those involved in cancer, and further Vijg II teaches an example with p53. Further, Vijg II teaches in great detail how to optimize experimental conditions and primer sequences and even teaches a computer assisted method to determine optimum experimental conditions and primer sequences, for example Vijg II teaches generating "trial melting profiles" for the primers and GC clamps (see claim 1; also pp cols 6-14) using the improved computer assisted method developed by Vijg II. For example, Vijg II teaches that fragments to be applied to the electrophoresis should have a size and melting temperature unique to all other fragments included in the same test (see col. 6). Shattuck-Eidens

was cited to illustrate the fact that mutations in BRCA1 were known to be linked to breast and ovarian cancer at the time of the invention and to show why one of ordinary skill in the art would be motivated to detect mutations in BRCA1, due to its very well characterized link to cancer.

5/16/03 Therefore, armed with the teachings of Vijg & Vijg II, each in view of Shattuck-Eidens, the ordinary artisan would have been motivated to apply the improved method of identifying mutations of Vijg, or the computer aided method of Vijg II, to detect BRCA1 mutations, as taught by Shattuck-Eidens. In applying the method of Vijg or Vijg II in view of Shattuck-Eidens (that is on the BRCA1 gene), the ordinary artisan would have been able to generate a number of different primers and GC clamps that would have been able to be used to detect BRCA1 mutations, including the primers of the instantly claimed invention, that would be considered equivalent in a method of two dimensional gel electrophoresis, as taught by Vijg or Vijg II in view of Shattuck-Eidens, to the sequences of the instantly claimed invention, absent secondary considerations. It is further noted that the set of primers for use in the invention would be limited to primers that satisfied the criteria taught by Vijg or Vijg II, and that one would not expect the ordinary artisan to determine what the sequences of the primers could be without following the detailed directions and criteria set out by both Vijg and Vijg II to obtain primers for use in the method of Vijg or Vijg II in view of Shattuck-Eidens. The response further cited Ahern as illustrating why the ordinary artisan would be motivated to package such primers in kit format, for the convenience and time saving effects it would provide to researchers. Accordingly, the response's question as to how the primers of the instantly claimed invention would "somehow obviously jump out" is not sufficient to overcome the rejection because the rejection in the previous office action, and set forth above does not suggest that the primers

would be immediately apparent without some experimental manipulation, which is taught by Vijg and specifically illustrated by the teachings of Vijg II. With regard to the response's question as to "where has the Office demonstrated that these very specific primer sequences result", applicant is directed to the 103 rejection made above which sets forth the teachings of Vijg or Vijg II in view of Shattuck-Eidens.

The response further asserts that it is unclear how an ordinary artisan would obviously come up with precisely applicant's specific primer pairs of the presently claimed invention, that such is not explained and is further not a tenable or legal ground of rejection. This argument has been thoroughly reviewed but was found unpersuasive. To reiterate, the rejection applied above set forth that with the method of Vijg or Vijg II in view of Shattuck-Eidens, the ordinary artisan would have been able to generate a number of different primers and GC clamps that would have been able to be used to detect BRCA1 mutations, including the primers of the instantly claimed invention, that would be considered equivalent in a method of two dimensional gel electrophoresis, as taught by Vijg or Vijg II in view of Shattuck-Eidens, to the sequences of the instantly claimed invention, absent secondary considerations. It is further noted that the set of primers for use in the invention would be limited to primers that satisfied the criteria taught by Vijg and Vijg II, and that one would not expect the ordinary artisan to determine what the sequences of the primers could be without following the detailed directions and criteria set out by both Vijg and Vijg II to obtain primers for use in the method of Vijg or Vijg II in view of Shattuck-Eidens. If the prior art did not expressly teach how to develop primers and GC clamps for detecting mutations of any gene or provide a computer-assisted method that could be used with any gene, this argument would be persuasive. However, in the instant case, the cited prior

art, which is applicant's own work, is very specific with regard to criteria and experimental manipulations required to apply the method taught by Vijg or Vijg II, to any gene. As the sequence of the BRCA1 gene was known in the art at the time of the invention, and further, it was known that mutations in BRCA1 were linked to cancer, the ordinary artisan would have been capable of and motivated to apply the teachings of Vijg or Vijg II to obtain primers and clamping sequences that could be used to detect mutations in the BRCA1 gene.

The response asserts that it is the duty of the office to show anticipation and not just to guess that routine experimental manipulation would automatically and obviously lead to "the specific primer pairs of the presently claimed invention". This argument has been thoroughly reviewed but was found unpersuasive. Firstly, it is noted that the previous office action as well as the rejection set forth above were applied under 35 USC 103 and not 35 USC 102. Anticipation is not a criterion for rejections under 35 USC 103, but rather for 35 USC 102 rejections. Secondly, the examiner did not "guess" that routine experimental manipulation would automatically and obviously lead to "the specific primers of the presently claimed invention". The rejection sets forth that Vijg teaches criteria and conditions to carry out the method and Vijg II teaches in detail, including a computer assisted method which would the ordinary artisan as to how and where to pick primers for each step of the method, as well as GC clamps for use in the method of Vijg and Vijg II. Vijg teaches that experimental manipulations are required (see pp 6-9). Further the teachings of Vijg II specifically illustrate that experimental manipulations are required to obtain primers for use in the method of Vijg II in view of Shattuck-Eidens. Armed with such teachings, the ordinary artisan would have been capable of generating a number of different primers and GC clamps that would have been able to be used to detect

BRCA1 mutations, including the primers of the instantly claimed invention, that would be considered equivalent in a method of two dimensional gel electrophoresis, as taught by Vijg or Vijg II in view of Shattuck-Eidens, to the sequences of the instantly claimed invention, absent secondary considerations. A showing, in declaration format (see MPEP 716.02 (g)), that the primers of the instantly claimed invention were further manipulated in ways not taught by Vijg or Vijg II, would overcome the rejection. [It is noted that a declaration was filed in the response of October 25, 2000, however, as stated in the office action dated December 19, 2001, the manipulations set forth in the declaration were taught by Vijg and Vijg II. To reiterate: the declaration set forth that it was necessary to require the splitting of the BRCA1 gene into fragments, for example exon 11 was split into 16 different fragments. This was not found persuasive as Vijg specifically teaches that fragments for electrophoresis should be between 100 and 600 nucleotides long (see Vijg, p 14, lines 1-2). Further, the declaration set forth that clamps of variable sequence and links were found to be necessary to induce a stable melting domain, specifically the pairs of clamping units shown for exons 11.1... etc in Table 4". Further, the declaration points to Figs 1A and 1B as a showing of rather remarkable resolution. This was not found persuasive. Firstly, it was noted that the identification of clamping sequences with SEQ ID NOS and the pairing of such with regard to primers of table 4 are directed to new matter (see objection to the specification set forth above). Secondly, with regard to using clamps of variable sequence, both Vijg and Vijg II teach using clamps of varying sequence (See Vijg II, claim 2 and 4; and Vijg: Table 2- GCI, GCII, and GCIII correspond to a 30mer, 38mer, and 35mer respectively) and Vijg II specifically teaches using one or two clamps (see claims 4 and 5). The declaration also stated that the figures showed the remarkable resolution that could be obtained

using the primers of the instant invention. This was not found persuasive because no basis for comparison has been set forth illustrating the improved and "rather" remarkable clarity, resolution and reliability of these photos. Also, the specification provides no basis that these photos represent unexpected and improved resolution, such that no comparison can be made to assess these unexpected and improved results.]

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The response asserts that the 1999 paper cited, of Dr Vijg's (Orsouw et al) work, with the preliminary amendment of 8/2/1999 shows the "totally unexpected" result as claimed by applicant's specific primer pairs. The response asserts that the specific and novel sequences of applicant led to the discovery of an additional five mutations that had previously escaped detection with prior BRCA1 detection systems and that the abstract discloses that "in addition to the 19 mutations, a total of 15 different polymorphic variance were scored, most of which were recurring", which was "hardly obvious". This argument, as well as the Orsouw et al reference have been thoroughly reviewed, but were found unpersuasive to overcome the rejection. Upon a thorough review of the Orsouw et al reference, it appears that the " additional five mutations" were already known in the prior art (see p. 750, col. 2, lines 8-27), but had escaped detection

when the authors compared the analysis of mutations using the primers and TDGE method of Vijg and Vijg II with other prior art methods of detecting mutations, such as the protein truncation test as well as partial nucleotide sequencing (see p. 750, col. 1, first full para). To show unexpected results, however, applicant is required to compare the claimed invention with the closest prior art, which in this case, are the teachings of Vijg and Vijg II. Given that Vijg teaches that the TDGE method using long and short PCR with GC clamps provides "efficient and accurate examination for mutations", (see p. 2 of Vijg, lines 5 and 6), the ordinary artisan would have expected that the method of Vijg or Vijg II in view of Shattuck-Eidens would have yielded more accurate and efficient analysis than other prior art methods. MPEP 716.02 (b) states under "Direct and Indirect Comparative Tests are Probative of Nonobviousness:

"Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims.";

and MPEP 716.02(e) states:

"Comparison With Closest Prior Art: An affidavit or declaration under 37 CFR 1.132 must compare the claimed subject matter with the closest prior art to be effective to rebut a prima facie case of obviousness. In re Burckel, 592 F.2d 1175, 201 USPQ 67 (CCPA 1979). "A comparison of the claimed invention with the disclosure of each cited reference to determine the number of claim limitations in common with each reference, bearing in mind the relative importance of particular limitations, will usually yield the closest single prior art reference." In re Merchant, 575 F.2d 865, 868, 197 USPQ 785, 787 (CCPA 1978) (emphasis in original). Where the comparison is not identical with the reference disclosure, deviations therefrom should be explained, In re Finley, 174 F.2d 130, 81 USPQ 383 (CCPA 1949), and if not explained should be noted and evaluated, and if significant, explanation should be required. In re Armstrong, 280 F.2d 132, 126 USPQ 281 (CCPA 1960) (deviations from example were inconsequential)."

In addition, it is noted that Orsouw et al does not teach any specific primer sequences or GC clamps. However, were the primer sequences used by Orsouw et al the same as the instantly claimed invention, MPEP 716.02(d) states that "Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the 'objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support.'" Orsouw et al teach that the detection of the mutations was achieved with a 7 plex

long distance PCR from total genomic DNA, followed by multiplex short PCR in 4 multiplex groups, and lastly with electrophoresis. However, none of the kit claims list any specific combination of primers or GC clamps, and none of the method claims are directed to all the primers and GC clamps presumably used in the Orsouw et al method (presumably all of the primers of table 4). Further, the instantly filed specification is silent with respect to the identity (that is the exact sequences) of GC clamps used in the method of detecting BRCA1 mutations outlined in the specification (the pairing of GC clamp sequences with primers in table 4 constitutes new matter as this disclosure was not present in the specification as originally filed, see Specification objection above).

Conclusion

13. No claims are allowable.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703) 308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya

Jehanne Souaya
Patent examiner
Art Unit 1634
5/16/03